## REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated May 3, 2007 are respectfully requested.

I. Amendments

Claim 43 is canceled.

No new matter is added by way of these amendments.

II. Claim Identifiers

Applicants have amended the claim identifiers to properly reference claims 26-33, 37-39, and 41 as canceled as recited in Applicants' response mailed July 29, 2005. It is Applicants' understanding that the claim identifiers in the above claims are correct.

III. Rejections under 35 U.S.C. §112, first paragraph

Claims 1-7, 10, 34-36, and 40 were rejected under 35 U.S.C. § 112, first paragraph, for lack of written description.

Claims 1-7, 10, 34-36, and 40 were further rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification does not enable any person skilled in the art to which it pertains, or with which it is most connected to make and use the invention commensurate in scope with the claims.

These rejections are respectfully traversed.

A. Written Description

The Examiner asserts that the specification fails to provide an adequate written description of the invention as claimed. The claims, as amended, are directed to an assay method for determining binding of a test agent and a lipid-bilayer-associated component associated with a lipid bilayer expanse of the array device. The membrane fluidity of one or more of the lipid expanses is changed by this binding. The membrane fluidity is evaluated and binding of the test agent to

the lipid bilayer-associated component is correlated to a change in membrane fluidity.

As noted above, the present method comprises the steps of (i) providing a surface detector array device, (ii) contacting the device with a bulk aqueous phase comprising a test agent, whereby the membrane fluidity of one or more lipid bilayer expanses changes when the test agent binds to the lipid bilayer-associated component, and (iii) evaluating the membrane fluidity of one or more of the lipid bilayer expanses.

With regard to step (i), surface detector array devices are described on page 9, lines 15-31 and an exemplary device is shown in Fig. 1.

With regard to (ii), contacting the device with a bulk aqueous phase comprising a test agent and detecting the binding of the test agent to the lipid bilayer-associated component through their effects on the membrane fluidity of the lipid bilayer is described on page 14, line 8. Methods for measuring and evaluating the membrane fluidity are described on page 14, line 19 through page 15, line 15.

The Examiner states that there is no disclosure of the claimed genera of test agents and lipid bilayer-associated components beyond the disclosure of cholera toxin subunit B (CTB) and ganglioside GM1. Applicants respectfully remind the Examiner that the claimed method is an assay for determining binding. The purpose of the assay is to determine binding. Therefore, Applicants should not need to show test agents and lipid-bilayer-associated components to which they know will bind. Applicants have shown that binding of a test agent to a lipid bilayer-associated component does effect a change in the membrane fluidity (Example 6).

The Examiner states that "at issue is whether all binding events would result in detectable changes in membrane fluidity" (page 10, Office action mailed May 3, 2007). Applicants respectfully disagree. As the present claims are directed to an assay method, at issue is whether the assay positively detects those binding interactions that result in a change in membrane fluidity. All assays have the potential for "false positives" and "false negatives" and there are numerous reports of viable assays with such "false positive" and/or "false negatives." For example,

Evans *et al.* (BMJ, 315:772-774, 1997, copy enclosed) discuss the false negative results obtained with an HIV antibody assay. Further, Imai *et al.* (Int Conf AIDS, 10:242, abstract PB0399, 1994, enclosed herewith) state a "[m]ajority of HIV antibody screening positive samples showed false positive reaction" by several assays. These assays are still viable for what they do detect.

Examiner Foster further invited Applicants to submit publications showing that other test agents cause a change in membrane fluidity when bound. In addition to the several articles discussed by the Examiner, Applicants submit seven articles (enclosed herewith) demonstrating the effects of diverse small molecules and peptides on membrane fluidity:

Carrier et al., Biochemical Pharmacology, 53:401-408, 1997.

Hashimoto et al., Journal of Lipid Research, 42:1160-1168, 2001.

Kremer et al., Biochemistry, 39:10309-10318, 2000.

Ohyashiki et al., J. Biochem., 111:419-423, 1992.

Pezeshk et al., Life Sciences, 63:1863-1870, 1998.

Tsuchiya et al., Clinical and Experimental Pharmacology and Physiology, 28:292-299, 2001.

Abu-Salah, Biochemical Pharmacology, 42:1947-1951, 1991.

As shown in these references, small molecules and short peptides with vastly different structures, functional properties, and applications all have measurable effects on membrane fluidity. These molecules represent a fair sampling of the universe of possible test agents which may be encountered during the drug screening process, which is one important application of this invention. Specifically, the effects are:

1. amyloid-beta (39-40 amino acid peptide) decreases fluidity;
2. daunomycin (a chemotherapeutic agent) decreases fluidity;
3. amikacin (antibiotic) decreases fluidity;
4. kanamycin A and B (antibiotics) decreases fluidity;
5. propofol (sedative) increases fluidity;
6. docosahexenoic acid (fatty acid present in membranes) increases fluidity;

7. malondialdehyde (lipid degradation product) decreases fluidity;
8. amphotericin B (antifungal agent) increases fluidity;
9. nystatin (antifungal agent) increases fluidity;
10. valinomycin (peptide antibiotic) decreases fluidity;
11. gramicidin A (peptide antibiotic) decreases fluidity;
12. procaine (local anesthetic) decreases fluidity.
13. althesin (general anesthetic) increases fluidity
14. propanidid (general anesthetic) increases fluidity

An exemplary, and potentially important, use of the claimed method is in screening of large libraries of compounds as potential therapeutic agents. Binding of potential agents to a lipid bilayer component is an indicator of therapeutic activity.

Finally, the Examiner is directed to Example 12 of the USPTO Written Description Guidelines. Recognizing that the scenario is a computer implemented method, the case is analogous to the present method in that both are directed to determining a result by detecting an interaction. In accord with the Guideline scenario, providing a surface detector array device was known in the art as evidenced by U.S. Patent No. 6,228,326 and methods for evaluating membrane fluidity are known in the art. Further, the present specification provides guidance for evaluating the membrane fluidity. In contrast to the Guideline scenario, the present application provides an actual reduction to practice as well as a clear depiction of the claimed assay.

In view of the teachings in the specification, the level of skill, and the knowledge in the art, one skilled in the art would reasonably conclude that Applicants were in possession of the claimed invention at the time the invention was filed.

B. Enablement

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent enable any person skilled in the art to which it pertains to make and use the

claimed invention without undue experimentation (e.g., *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The enablement requirement is met if the description enables any mode of making and using the claimed invention (*Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 20 USPQ2d 1300 (Fed. Cir. 1991).

As noted above, the amended claims are directed to a method for assaying an interaction between a test agent and a lipid bilayer-associated component using a surface detector array device including a plurality of lipid bilayer expanses. When the test agent binds to the lipid bilayer-associated component, the membrane fluidity of the lipid bilayer expanse(s) is changed. Example 7 of the present invention provides guidance for an exemplary test agent and lipid bilayer-associated component, specifically the cholera toxin and the ganglioside GM1 membrane target. Applicants have provided literature support for fourteen additional small molecules/peptides that cause a change in fluidity upon interacting with the cell membrane.

The Examiner noted that "the prior art teaches that integral membrane proteins in supported bilayers may often be non-functional, and therefore incapable of interacting with test agents" (Office action page 10). While this may be true, the same reference cited by the Examiner lists a number of standard methods known in the art to enhance the activity of integral membrane proteins. One exemplary method relies on the use of polyethylene glycol cushions to enhance the mobility and activity of integral membrane proteins (Wagner ML and Tamm L (2000) *Biophys J*, 79: 1400-1414) (enclosed herewith). It is noted that this article is referenced as one possible method for enhancing the activity of integral membrane proteins and is not an essential feature of the presently claimed assay.

The Examiner further states "From the above teachings of Boxer et al., this may indicate that CTB is non-functional, and would therefore be incapable of interacting with test agents. This would be of particular relevance to claim 3, in which bacterial endotoxins may be the lipid bilayer-associated component that interacts with test agents" (see page 9, Office action mailed May 3, 2007).

Applicants respectfully remind the Examiner that CTB is an exotoxin - a protein secreted by the bacterium - not an endotoxin as recited in claim 3. In other words, CTB functions as the test agent, rather than as the lipid bilayer-associated component.

In determining enablement, the courts have identified several Wands factors to be considered:

*(i) The nature of the invention and (ii) breadth of the claims*: Claim 1 as amended relates to a method for assaying an interaction between a test agent and a lipid bilayer-associated component. The method comprises (i) providing a surface detector array device comprising; (ii) contacting the device with a bulk aqueous phase comprising the test agent that specifically binds to the lipid bilayer-associated component, whereby the membrane fluidity of at least one of the plurality of lipid bilayer expanses changes when the test agent binds to the lipid bilayer-associated component; (iii) evaluating the membrane fluidity of one or more of lipid bilayer expanses, and (iv) detecting binding of the test agent to the lipid bilayer-associated component by correlating a change in membrane fluidity to binding.

*(iii) The state of the prior art and (iv) the predictability of the art:* At the time of the invention, a surface detector array device was known as evidenced by U.S. Patent No. 6,228,326. Further, methods for evaluating membrane fluidity were known in the art as also known from the '326 patent.

*(v) The amount of direction or guidance presented and (vi) the presence or absence of working examples*: Evaluating membrane fluidity is known in the art and described in the specification page 14, line 19 through page 15, line 15. Example 6 in the application provides working details to conduct such tests.

*(vii) The quantity of experimentation necessary*: The present method is directed to assaying an interaction between a test agent and a lipid bilayer associated component. The present application provides ample guidance for any experimentation necessary in the present method.

Accordingly, Applicants submit that the specification would enable any person skilled in the art to which it pertains to make and use the claimed invention.

In light of the above, Applicants submit that the present claims satisfy the requirements of 35 U.S.C. §112, first paragraph and respectfully request that the rejections be withdrawn.

IV. Conclusion

Applicants respectfully submit that the pending claims are in condition for immediate allowance. The undersigned invites the Examiner to call (650) 838-4410 with any questions or comments. The Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. 50-2207.

Respectfully submitted,
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